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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,565	10/17/2001	Thomas J. Gardella	0609.4730000	4604

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,565	GARDELLA ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20 and 22-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *25 and 26* is/are allowed.

6)☒ Claim(s) *20,22-24,27 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 12/1/05 has been entered in full. Claims 20 and 24-28 are amended. Claims 1-19 and 21 were canceled previously by Applicants.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20 and 22-28 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (8/1/05).

The rejection of claims 20, 22-28 under 35 U.S.C § 112, second paragraph, at pg 12 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims, and persuasive arguments with regard to rΔNt being the scientific name of the claimed receptor.

Please see the new rejection under 35 U.S.C § 112, 2nd paragraph, below.

Claim Rejections - 35 USC § 112, 1st paragraph, scope of enablement

Claims 24 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method using cells comprising a polynucleotide encoding a polypeptide at least 95% identical to SEQ ID NO: 2, does not reasonably provide enablement for a polynucleotide at least 95% identical to a nucleotide sequence from about position 1 to about position 1320 in SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection was set forth at pg 3-8 of the 8/1/2005 Office Action.

Applicants' arguments (12/1/05; pg 13-14) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated 12/1/05, Applicants submit that the claims clarify that the polynucleotides are variants of SEQ ID NO: 1, and request that the rejection be reconsidered and removed.

Applicants' arguments have been fully considered but are not found persuasive. The claims are not enabled for variants that are 95% identical to a nucleotide sequence from position 1 to position 1320 in SEQ ID NO: 1. The reasons for this were set forth previously (8/1/05) and are reiterated herein:

The open coding region of SEQ ID NO: 1 is 1305 nucleotides (from residue 1 to 1305). The genus of polynucleotides that are at least 95% identical to a sequence of 1305 nucleotides encompasses those with 1240 or more identical nucleotides. In other words, up to 65 nucleotides can be changed in the coding sequence of SEQ ID NO: 1 and still have a polynucleotide at least 95% similar to SEQ ID NO: 1. The genus includes those polynucleotides in which each of the 65 nucleotide changes are in a different codon. Therefore, the genus encompasses those polynucleotides that encode polypeptides with up to 65 different amino acids in SEQ ID NO: 2, which is a polypeptide of 435 amino acids. In other words, this genus encompasses polynucleotides encoding polypeptides having 370 out of 435 amino acids found in SEQ ID NO: 2, or at least 85% similarity.

While the specification teaches the functionality of a receptor of SEQ ID NO: 2, the breadth of the claims is such that the claims encompass a method using variants in which one or more amino acids of SEQ ID NO: 2 are substituted, deleted, and/or inserted. Claims 24 and 27 encompass a polynucleotide encoding a polypeptide that comprises an amino acid sequence that is at least 85% similar to SEQ ID NO: 2 (as explained above), and can increase intracellular cAMP levels when activated by PTH or PTH-related peptide.

Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of polypeptides of SEQ ID NO: 2. The specification has not provided a working example of the use of a variant of the

polypeptide of SEQ ID NO: 2, nor sufficient guidance so as to enable one of skill in the art to make such a variant. The specification has failed to teach which amino acids of SEQ ID NO: 2 could be modified so as to produce a polypeptide that is not identical to SEQ ID NO: 2 and yet still retain a characteristic of the parent polypeptide, e.g., the functionality of increasing intracellular cAMP levels when activated by PTH or PTH-related peptide.

Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the protein corresponding to SEQ ID NO: 2 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 2 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 2. Conversely, if a protein variant of SEQ ID NO: 2 need not have a disclosed property, than the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [the references of Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495; both

references were cited in the previous Office Action]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427; each of these references was cited in the previous Office Action].

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the

breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 24 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 8-11 of the 8/1/05 Office Action.

Applicants' arguments (12/1/05; pg 14) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated 12/1/05, Applicants submit that the claims to clarify that the polynucleotides are variants of SEQ ID NO: 1 and request that the rejection be reconsidered and removed.

Applicants' arguments have been fully considered but are not found persuasive. The claims lack written description for a genus of variants that are 95% identical to a nucleotide sequence from position 1 to position 1320 in SEQ ID NO: 1. The reasons for this were set forth previously (8/1/05) and are reiterated herein:

The open coding region of SEQ ID NO: 1 is 1305 nucleotides (from residue 1 to 1305). The genus of polynucleotides that are at least 95% identical to a sequence of 1305 nucleotides encompasses those with 1240 or more identical nucleotides. In other words, up to 65 nucleotides can be changed in the coding sequence of SEQ ID NO: 1 and still have a polynucleotide at least 95% similar to SEQ ID NO: 1. The genus includes those polynucleotides in which each of the 65 nucleotide changes are in a different codon. Therefore, the genus encompasses those polynucleotides that encode polypeptides with up to 65 different amino acids in SEQ ID NO: 2, which is a polypeptide of 435 amino acids. In other words, this genus encompasses

polynucleotides encoding polypeptides having 370 out of 435 amino acids found in SEQ ID NO: 2, or at least 85% similarity.

Therefore, claims 24 and 27 are genus claims because the claims are directed to methods of using cells encompassing polynucleotides encoding polypeptides with 85% or greater similarity to SEQ ID NO: 2, wherein the polypeptide increases intracellular cAMP levels when activated by PTH or PTH-related peptide. The genus of encoded polypeptides is highly variant because a significant number of structural differences between genus members are permitted. However, the instant specification fails to describe the entire genus of methods that are encompassed by each of these claims.

From the specification, it is clear that Applicants has possession of method of using a cell comprising a polynucleotide encoding SEQ ID NO: 2. The specification fails to describe or teach any other polypeptide which lacks the sequence of SEQ ID NO: 2 and increases intracellular cAMP levels when activated by PTH or PTH-related peptide. The claims, however, are not limited to a method of using a polynucleotide encoding SEQ ID NO: 2.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides encoded by the polynucleotides used in the claimed methods. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The

general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.
One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods using cells comprising a nucleic acid encoding SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35

U.S.C. §112, first paragraph. Applicants are reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 2nd paragraph

Claims 20, 22, 23, 24, 27 and 28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is newly set forth but is necessitated by Applicants' amendments to the claims.

Claims 20, 24, 27 and 28 are indefinite because each claim, as amended, recites the following:

"...wherein said polypeptide increases intracellular cAMP levels when activated by PTH or PTH-related peptide extracellular amino-terminal ligand binding domain has an amino acid sequence from about residues 26 to about residue 181 in wild type PTH receptor..."

The examiner cannot determine the exact meaning of this phrase. It is noted that in the 5/13/05, said phrase was presented as, "...wherein said polypeptide increases intracellular cAMP levels when activated by PTH or PTH-related peptide and wherein said extracellular amino-terminal ligand binding domain has an amino acid sequence from about residues 26 to about residue 181 in wild type PTH receptor..." (emphasis added to demonstrate the difference between the two phrases.) It is suggested that Applicants perhaps inadvertently left out part of the phrase when preparing the current claim set. However, the meaning of this phrase in the current claims is unclear.

Claims 22 and 23 are indefinite for the same reason because they depend from claim 20.

Claim Rejections - 35 USC § 102

Claims 20, 22, 23 and 28 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by U.S. Patent No. 5,494,806 (cited previously by the Examiner on the PTO-892 of 2/12/2004). This rejection was set forth at pg 13-14 of the 8/1/05 Office Action.

Applicants' arguments (12/1/05; pg 15) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated 12/1/05, Applicants submit that the '806 patent does not anticipate the claimed invention because it does not teach each every claim limitation. Applicants argue that the Examiner does not take into account the deletion of the extracellular amino-terminal ligand binding domain in the alignment. Applicants argue that if this deletion was taken into account, the percent identity would be vastly reduced because of the absence of 155 amino acids between the two sequences.

Applicants' arguments have been fully considered but are not found persuasive. The '806 patent does teach every claim limitation of rejected claims for the following reasons. A sequence alignment between instant SEQ ID NO: 2 and SEQ ID NO: 3 of the '806 patent was provided with the 8/1/05 Office Action (see Sequence Alignment #1), showing 96.1% identity between the two sequences. Said alignment did take into account the deletion of the extracellular amino-terminal ligand binding domain. It is again noted that the sequence that Applicants have submitted as SEQ ID NO: 2 *is* the parathyroid hormone receptor with the extracellular ligand binding domain deleted. Therefore, an alignment using instant SEQ ID NO: 2 inherently takes into account the deletion of the extracellular ligand binding domain. Furthermore, the alignment algorithm parameters used by the Examiner were reasonable parameters for one of skill in the art to use to align two protein sequences. As shown in the alignment, the BLOSUM62 scoring table was used with a gap opening penalty of 10.0 and a gap extension penalty of 0.5. Sunyaev et al (2004) teaches similar parameters for use in protein sequence alignments (see pg 572 of Sunyaev et al. 2004. Proteins: Structure, Function and Bioinformatics. 54: 569-582.) Furthermore, Vogt et al (1995) teaches that the optimized gap opening and extension penalties for CLUSTAL62 are, respectively, 10.00 and 0.60 (see Table 8 on pg 822 of Vogt et al. 1995. J Mol Biol. 249: 816-831.) Applicants' claims do not limit the algorithm or parameters by which the 95% percent identity is calculated. Therefore, it is appropriate for the Examiner to use an algorithm with a set of parameters that one of skill in the art would reasonably use to align two sequences.

Claim 20 is drawn to a method of screening for an agonist or antagonist of PTH receptor activity comprising contacting cells expressing a genus of rΔNt polypeptide with a test compound. The genus of rΔNt polypeptide encompassed by the claim includes any polypeptide that is at least 95% identical to the sequence from "about position 1 to about position 435 in SEQ ID NO: 2, wherein the extracellular amino-terminal ligand binding domain is deleted." The extracellular binding domain is further defined in the claim as having "an amino sequence from about residue 26 to about residue 181 in wild-type PTH receptor." However, as indicated in the specification, SEQ ID NO: 2 is the sequence of the wild-type PTH receptor with said domain deleted. Therefore, the phrase "wherein the extracellular amino-terminal ligand binding domain is deleted" does not in any way further modify SEQ ID NO: 2, because this is an inherent characteristic of SEQ ID NO: 2. Furthermore, position 1 to position 435 represents the entire sequence of SEQ ID NO: 2. Therefore, the genus of rΔNt polypeptides encompassed by the claim includes any polypeptide that is at least 95% identical to SEQ ID NO: 2.

The '806 patent teaches SEQ ID NO: 3, which is a nucleic acid sequence encoding a rat PTH receptor amino acid sequence that is 96.1% identical to instant SEQ ID NO: 2 (an alignment of these sequences was attached to 8/1/05 Office Action as Sequence Alignment #1). The '806 patent further teaches that the PTH receptor stimulates cAMP accumulation when activated PTH (see col 9, lines 14-15). The '806 patent further teaches screening assays to test compounds for agonistic or antagonistic properties using the cAMP accumulation (see col 22, lines 65-67). Therefore, the '806 patent clearly anticipates instant claims 20, 22 and 23.

Claim 28 encompasses a method with the same limitations as claim 20, except that the test compound is iodinated and the method comprises determining whether the iodinated test compound competitively binds to the receptor. The '806 patent teaches using iodinated PTH analogs in the screening method (see col 22, line 55) and determining whether test compounds compete for PTH binding (see col 23, lines 11-12), clearly anticipating claim 28.

Conclusion

Claims 25 and 26 are allowable.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JANET L. ANDRES
SUPERVISORY PATENT EXAMINER